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Office Action Summary	Application No.	Applicant(s)
	09/647,309	ANDREONI ET AL.
	Examiner Khatol S Shahnam-Shah	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 08 April 2003.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 22-40 is/are pending in the application.

4a) Of the above claim(s) 40 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 22-39 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) 22-40 are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____	6) <input type="checkbox"/> Other: _____

DETAILED ACTION

1. Applicants' response and election received 4/8/2003, paper # 14 is acknowledged.

Election/Restriction

2. Applicants elected with traverse Group III (claims 22-39) that is drawn to use of an enterobacterium membrane protein as a nasal composition. Applicants elected species antigen, RSV virus and SEQ IDS 2 and 136. The examiner noted applicants' comment in regard to claims 1-21, which were canceled upon submission of a preliminary amendment filed September 27, 2000, which inadvertently was missed by the office. Those claims are canceled now and restriction of group I, directed to claims 1-21, is thereby rendered moot.
3. Claims 22-40 are pending in this application. Claim 40 is withdrawn from consideration as being drawn to a non-elected invention.
4. Claims 22-39 are under consideration.

Objections Withdrawn

5. Objection to the drawings made in paragraph 12 of the office action mailed 2/11/2003 is withdrawn in view of applicants' amendment. New corrected drawings were submitted and the drawings are acceptable.

Objections Maintained

6. Objection to the abstract made in paragraph 11 of the office action mailed 2/11/2003 is maintained. Applicants' comment in regard to the abstract, which is printed on the cover of the PCT pamphlet, is noted. The cover of PCT pamphlet contains two abstracts one in English and one in French. It will be more appropriate for the applicants to submit the proper abstract. Applicants' cooperation will be appreciated in this regard.

7. The objection to the priority statement made in paragraph 10 of the office action mailed 2/11/2003 is maintained. Priority statement is required in the first page of the specification. The applicants apparently misunderstood examiners request in this matter. Also the full translation of the foreign document is required. Should applicants desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application No. 98/03814 should be submitted under 37 CFR 1.55 in reply to this action. At this time the priority date granted is 3/26/1999.

New Objection

Specification

8. The disclosure is objected to because of the following informalities: This specification contains sequences in the specification which does not comply to 37 CFR 1.821 (d) for failing to reference to the sequences by use of sequence identifiers, preceded by "SEQ ID NO" in the text of description (see page 7, line 36). Appropriate correction is required

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 22-39 provide for the use of at least one fragment of a membrane protein, but, since the claims do not set forth any steps involved in the method/process, it is unclear what

method/process applicants are intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 22-39 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of rP40 protein of *Klebsiella pneumoniae* does not reasonably provide enablement for use of other enterobacterium proteins and its fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make /or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP) 2164.01(a). Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples (6) the quantity of experimentation, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The claims are drawn to use of at least one fragment of a membrane protein of an enterobacterium. The specification only describes use of a membrane protein from *Klebsiella pneumoniae*. The claims are broadly drawn to use of membrane proteins of enterobacteria which include numerous genus and species. Use of one specific species of one enterobacterium does not necessarily include all of them.

The claims of the instant application are not only drawn to isolated immunogenic proteins but are also drawn to fragments of the proteins. The specification only discloses a fragment corresponding to rP40 of *Klebsiella pneumoniae* strain IP I 145 (see page 7, example 1).

Claim 25 recites use of a fragment, which has the sequence SEQ. I.D. NO 2. The specification fails to describe where this sequence comes from and how this fragment can be used. There is no guidance provided as to which fragment would be effective as a pharmaceutical composition. There is no guidance provided in the specification as how one would begin to choose “at least one fragment”.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein’s amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein’s sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins’ structure relates to its function. However, the problem of prediction protein structure from mere

sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure.

One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins.

The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- an amino acid sequence for the claimed protein;
- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which retain the biological activity if the intact protein; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen Inc v. Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed.Cir.1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546(Bd. Pat. App. & Int. 1986).

In view of all of the above, it is determined that it would require undue experimentation to make and use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 22-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Rauly et al. (Reseach in Immunology, Vol. 149, No.1, pp. 99, January 1998). Prior art of record.

Claims are drawn to a composition comprising at least one fragment of a membrane protein. The composition according to claims 22 is intended to be used as a pharmaceutical

composition intended to be administered nasally. However, intended use does not impart any critical impact or weight on the physical preparation and the patentability of the product.

Rauly et al. teach using an outer membrane protein (OmpA) of *Klebsiella pneumoniae* for enhancing or improving immunity of a mammal with respect to an antigen (see page 99). Rauly et al. teach a protein obtained by recombinant process. Rauly et al. teach use of the G1 antigen of RSV coupled to rP40 protein of *Klebsiella pneumoniae* the same conjugate as the claimed invention. SEQ ID No. 2 and SEQ ID No. 136 will be inherent in the rP40 protein of *Klebsiella pneumoniae* and the G protein of RSV. Rauly et al. teach that the conjugate generated strong antibody response even in the absence of any adjuvant. The prior art teach the claimed invention.

Since the office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed composition and the composition of the prior art (i.e., that the composition of prior art does not possess the same material structure and functional characteristics of the claimed composition). See In re Best, 562 F.2 d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

15. Claims 22-39 are rejected under 35 U.S.C. 102(a) as being anticipated by Rauly et al. (European Journal of Biochemistry, Vol. 255, pp. 446-454, July 1998).

Claims are drawn to a composition comprising at least one fragment of a membrane protein. The composition according to claims 22 is intended to be used as a pharmaceutical composition intended to be administered nasally. However, intended use does not impart any critical impact or weight on the physical preparation and the patentability of the product.

Rauly et al. teach using an outer membrane protein (OmpA) of *Klebsiella pneumoniae* for enhancing or improving immunity of a mammal with respect to an antigen (see abstract). Rauly et al. teach a protein obtained by recombinant process (see cloning and expression page 447). Rauly et al. teach detergent Zwittergent 3-14 (see reagents page 447). Rauly et al. teach use of the G1 antigen of RSV coupled to rP40 protein of *Klebsiella pneumoniae* the same conjugate as the claimed invention (page 447). SEQ ID No. 2 and SEQ ID No. 136 will be inherent in the rP40 protein of *Klebsiella pneumoniae* and the G protein of RSV. Rauly et al. teach that the conjugate generated strong antibody response even in the absence of any adjuvant (see pages 448 and 451). The prior art teach the claimed invention.

Since the office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed composition and the composition of the prior art (i.e., that the composition of prior art does not possess the same material structure and functional characteristics of the claimed composition). See In re Best, 562 F.2 d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Conclusion

16. No Claims are allowed.
17. The prior art made of record and not relied upon is considered pertinent to applicants' disclosure.

Binz et al. WO 96/14415

Binz et al. WO 95/27787

Swiss -Prot: Accession Number P24017

Erdile et al. (Vaccine, Vol. 15, No: 9, pp. 988-995, June 1997)

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol S Shahnan-Shah whose telephone number is (703) 308-8896. The examiner can normally be reached on 7:30am-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F Smith can be reached on (703) 308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


Khatol Shahnan-Shah, BS, Pharm, MS

Biotechnology Patent Examiner

Art Unit 1645

June 13, 2003


RODNEY P SWARTZ, PH.D
PRIMARY EXAMINER